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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,163	05/11/2006	Deok-Hoon Park	DE1683	3283

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EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
05/13/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/579,163	PARK ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, PhD	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,6,7 and 12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,6,7 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 4-20-11 is acknowledged.

Claims included in the prosecution are 3, 6-7 and 12.

Upon consideration, the 112, 2nd paragraph rejection is withdrawn.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 3, 6-7 and 12 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant introduces the term, 'relatively uniform size and shape' in claim 3. This limitation has no support in the specification as originally filed and therefore, deemed to be new matter.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 3, 6-7 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Popp (US 2006/0029657) in combination with Foldvari (5,853,755), optionally in further combination with Needham (US 2002/0102298).

Popp discloses topical skin protectant compositions containing 0.05 to 5 % phospholipid (hydrogenated lecithin), 0.001 to about 1.5 % ceramide, 0.1 to 5 % squalane, 8 to 30 % triglyceride, 2 to 5 % phytosterol. Although Popp teaches the use of an essential fatty acid, the fatty acid is in the form of oil. The composition is prepared by heating the oil phase components at a temperature of 40-50 degrees, mixing with the aqueous phase at the same temperature and homogenizing the mixture at 3000 rpm (0030-0117; 0164; 0195-0210; examples and claims.). Since the method of preparation is the same, the presence of multilayered liposomes is implicit. What is lacking in Popp is the use of fatty acid as such.

Foldvari teaches multilamellar vesicles for topical delivery. The liposomes contain a phospholipid, a ceramide and fatty substances to enhance the strength of the lipid bilayers. These include cholesterol and fatty acids such as stearic acid (0.5 %). The compositions further include oil and an active agent. The hydrophilic solvents include ethanol. The method of preparation involves mixing the two phases together at 40 to 80 degrees and homogenizing the mixture (abstract, col. 4, lines 8-41; col. 5, line 1 through col. 7, line 3; col. 8, line 47 through col. 10, line 9; col. 11, line 1 through col. 12, line 35; Examples). What is lacking Foldvari is the inclusion of squalane.

To include a fatty acid in the compositions of Popp would have been obvious to one of ordinary skill in the art since Foldvari teaches that fatty acids enhance the

strength of the lipid bilayers. Alternately, to include squalane in the compositions of Foldvari would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since Popp teaches that squalane is a therapeutic ingredient for the skin and its routine incorporation in topical formulations. The criticality of the sizes now recited is unclear to the examiner since the sizes of the multilamellar vesicles could be controlled by the speed of the mechanical vibration or homogenization. The examiner cites US 5,660,856 (see col. 5, lines 47-67), 5,965,156 (see col. 5, line 53 through col. 6, line 7) and 6,689,381 (see col. 9, lines 30-47) in this context. One of ordinary skill in the art would expect sizes of the liposomes in Popp and Foldvari to be similar to the claimed sizes since the reference of Needham indicates that the hydration of the phospholipid with an aqueous medium would result in multilamellar vesicles having average sizes of 700 nm. It should be noted that according to instant specification, the sizes can between 200 to 5000 nm.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues the following:

> "Claim 3 is directed to a method and to a composition in which multilayered liposomes are formed by dissolving oil phase components comprising squalene, sterols, ceramide, neutral lipids or oils, fatty acids and lecithins, in an organic solvent, dissolving the aqueous phase components at 50°C to 75°C and then mixing the dissolved components by agitating the mixture at 500 - 9000 rpm without the use of a high-pressure homogenizer. This procedure forms multilayered liposomes in a particle size range of 800 - 10,000 nm provided squalene is present in the range of 0.1-10 wt.%, the sterols are in the range of 0.1-5 wt.%, the ceramide is in a range of 0.1-10 wt.%, the neutral lipids or oils are in an amount from 0.1-20 wt.%, fatty acids is present in an amount of 0.1-20 wt.% and lecithins are present in the amount of from 0.1-5 wt.%, based on the total weight of the liposomes. The presence of both fatty acids and squalene are critical to the method of the subject invention for forming multilayered liposomes which will remain stable and uniform in size within a narrow size range of 800 - 1000 nm and will not grow in size over a time period of less than one year as is known to be conventional.

> This was confirmed in accordance with examples 1, 2, 3 and 4 of the specification. Example 1 shows that the prepared multilayered liposomes having the wt.% composition recited in claim 3 will form in a narrow size range of 800-1000 nm and that the number of liposome layers formed will be in a range of between 3 - 20 as shown in Example 2. The number of liposome layers formed has been added as new claim 12.
>
> Example 3 shows the result of measuring the stability of the liposomes which confirms the finding that after 12 months, the liposomes remain uniform and in the same narrow size range when formed, and are thermodynamically stable. As indicated in Table 3, conventional multilayer liposomes are not stable, are not uniform in size and grow in size by more than 50% over time (comparative examples 1, 2 and 4).
>
> Example 4 of the subject invention confirms that the multilayer liposomes of the present invention as claimed have an excellent subcutaneous absorption rate (see Table 4).
>
> The Popp reference cited by the Examiner recites a composition excluding fatty acids and does not teach agitating the mixture without the use of a high-pressure homogenizer. Instead, the Examiner seems to believe that even though it does not teach fatty acids and is silent regarding the conventional use of a high-pressure homogenizer, it must somehow be implicit that multilayered liposomes will be formed of uniform size in a range between 800 - 1000 nm. However, without the presence of fatty acids and without a teaching of not using a high-pressure homogenizer, there is no basis for this assumption, and certainly no basis for using the concentration of components as claimed to yield multilayered liposomes in a narrow size range of between 800 - 1000 nm. This is neither expressly taught or implicit from the teaching of Popp.

These arguments are not found to be persuasive. Popp teaches not just the composition, but the method of preparation of the claimed liposomes. As pointed out before, the composition is prepared by heating the oil phase components at a temperature of 40-50 degrees, mixing with the aqueous phase at the same temperature. Although Popp does not use the term, 'agitating', he does use the 3000 revolutions per minutes for mixing; this speed falls within the claimed 500-9000 rpm. Applicant's arguments that both squalene and fatty acid are critical to the method of subject invention for forming multilayered liposomes which will remain stable and uniform in size within a narrow size range of 800-1000 nm and will not grow in size over a time period of less than one year as is known to be conventional are not persuasive since Popp

teaches the use of squalane and essential fatty acids. The examiner erroneously stated before that Popp teaches the use of essential fatty acids in the form of triglycerides; however, in paragraphs 0161 and 0163-0164 Popp lists triglycerides and essential fatty acids separately and suggests the inclusion of the fatty acids. In paragraph 0222 Popp states, "Specifically, the present preferred compositions remain unexpectedly stable in storage for periods including between about 3 and about 18 months". Therefore, applicant's arguments with respect to claimed stability are not persuasive. Since Popp contains the same components and prepared in the same way, contrary to applicant's arguments, it is still the examiner's position that it would have liposomes of same sizes and applicant has not shown that to be otherwise. Furthermore, the examiner has already cited the reference of Needham which shows that hydration of the phospholipids with an aqueous medium would result in multilamellar vesicles having average sizes of 700. Even assuming that they are not of the same sizes, according to instant claim 7, the liposomes are further subjected to high-pressure homogenization step which shows that the sizes claimed are not critical. Finally it should be pointed out that applicant has not presented any comparative studies with the prior art product.

Applicant further argues that there is no teaching in Popp or any suggestion in Popp for producing multilayered liposomes much less that multilayered liposomes can be stably produced without using a high pressure homogenizer by following the method steps in claim 3. According to applicants since there is no teaching in Popp of the conditions to prepare multilayered liposomes, and no teaching of a fatty acid component, the method of claim 3 is clearly not obvious from the teaching of Popp and

no basis exists for the allegation that this method is implicit.

These arguments are not persuasive. As already pointed out before it is well known in the art that multilamellar liposomes are produced when an amphiphilic lipid such as a phospholipid is hydrated or added with an aqueous medium which upon further sonication or high pressure homogenization convert into unilamellar vesicles or liposomes. The prior art submitted by applicant itself shows that liposomes are produced when amphiphilic lipid is combined with an aqueous medium ((JP 02-149336 and H08-509202). Furthermore, the reference of Foldvari shows the formation of liposomes when a phospholipid, a ceramide, cholesterol and phospholipid, an oil and an aqueous phase are mixed and homogenized. Therefore, one would expect the formation of multilayered liposomes by the procedure described by Popp. Secondly, Popp teaches simple mixing and not high pressure homogenization. Even assuming he did, the examiner points out that instant claim 7 recites the step of subjecting the composition to high pressure homogenization step; the reference of Foldvari teaches homogenization. As already pointed out the figure 3 of Foldvari clearly shows the multilayered nature of the liposomes formed.

Applicant argues that Foldvari teaching does not teach adding squalene, which is critical to the subject invention. Applicant further argues that there is no teaching in Foldvari that the liposomes will be relatively uniform size within the narrow range and be thermodynamically stable so as not to change in size or shape over time. The examiner has already pointed out that Popp's liposomes are stable up to 18 months. With regard

to applicant's arguments that Foldvari does not teach adding squalene, the examiner points out that Foldvari is combined for its teachings that the fatty substances such as stearic acid enhance the strength of lipid bilayers; Foldvari therefore, provides clear motivation to add a fatty acid to the composition of Popp, assuming that Popp does not teach fatty acid. If the strength of the lipid bilayers is enhanced, it would be obvious to one of ordinary skill in the art that the liposomes are stable.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, PhD whose telephone number is (571)272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S. Kishore/
Primary Examiner, Art Unit 1612

GSK